

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/131630/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Frei, Przemyslaw, Jones, D. Heulyn, Kay, Steven T., McLellan, Jayde A., Johnston, Blair F., Kennedy, Alan R. and Tomkinson, Nicholas C. O. 2018. Regioselective reaction of heterocyclic N-oxides, an acyl chloride, and cyclic thioethers. *Journal of Organic Chemistry* 83 (3) , pp. 1510-1517. 10.1021/acs.joc.7b02457 file

Publishers page: <http://dx.doi.org/10.1021/acs.joc.7b02457>
<<http://dx.doi.org/10.1021/acs.joc.7b02457>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.

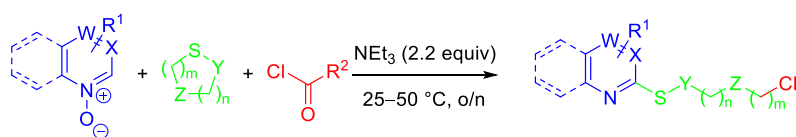


Regioselective Reaction of Heterocyclic *N*-Oxides, an Acyl Chloride and Cyclic Thioethers

Przemyslaw Frei,[†] D. Heulyn Jones,[†] Steven T. Kay,[†] Jayde A. McLellan,[†] Blair F. Johnston,[‡]
Alan R. Kennedy[†] and Nicholas C. O. Tomkinson^{†,*}

[†]WestCHEM, Department of Pure and Applied Chemistry, Thomas Graham Building, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, United Kingdom.

[‡]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, United Kingdom.



ABSTRACT: Treatment of electron deficient pyridine *N*-oxides with 4-nitrobenzoyl chloride and a cyclic thioether in the presence of triethylamine leads to the corresponding 2-functionalized product in up to 74% isolated yield. The transformation can also be accomplished with alternative nitrogen containing heterocycles including quinolines, pyrimidines, and pyrazines. To expand the scope of the transformation diisopropyl ether can be used as the reaction medium to allow for the use of solid thioether substrates.

Nitrogen containing heterocycles including pyridines, quinolines, pyrazines, and pyrimidines are embedded in many molecules of agrochemical and pharmaceutical significance.¹ Methods for either the generation or selective functionalization of these heterocycles are therefore of great interest.²⁻⁴ 2-Substituted derivatives represent an important subset of this family which show a broad spectrum of biological activities as exemplified by nexium, pirfenidone, boscalid, and lunesta (Figure 1) which contain carbon, oxygen, chlorine, and nitrogen substitution at the 2-position respectively.

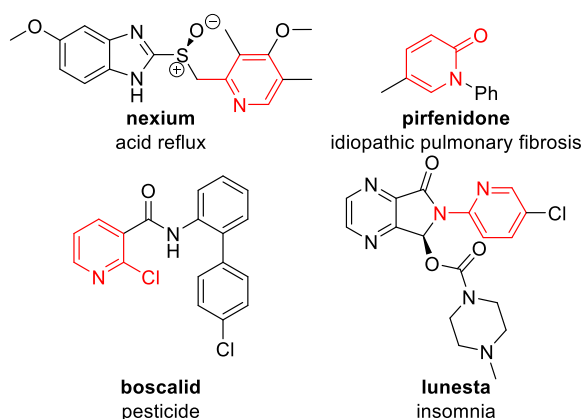


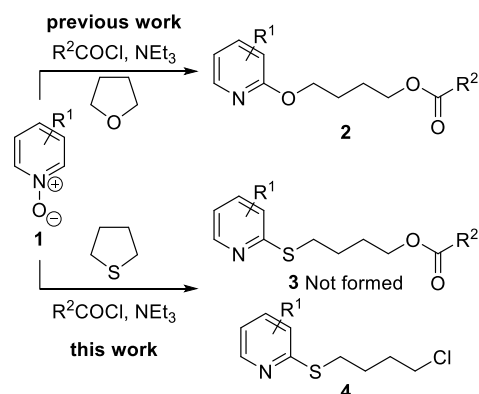
Figure 1. Examples of 2-heteroatom substituted pyridine derivatives with biological activity.

When compared to the introduction of nitrogen⁵ and oxygen⁶ heteroatoms at the 2-position of nitrogen containing heterocycles, the addition of a sulfur atom is a substantially less developed area. Two principal approaches have been developed for the introduction of a sulfur heteroatom: First, a S_NAr reaction on a 2-halo derivative, which is an effective strategy for electron deficient substrates.⁷ Second, the activation of heterocyclic *N*-oxides in the presence of a nucleophile. For example, PyBroP has been shown to be an excellent reagent to facilitate the addition of a thiol to the 2-position of a pyridine *N*-oxide.⁸ More recent methods for the sulfonylation of quinoline and pyridine *N*-oxides through reaction with sodium sulfonates,⁹ sulfonyl hydrazides,¹⁰ or sulfonyl chlorides¹¹ have further expanded this toolbox.

We recently described a simple and effective regioselective three-component coupling reaction of a pyridine *N*-oxide **1**, an acyl chloride and THF which led to the corresponding 2-functionalized pyridine **2** (Scheme 1).¹² We were interested to discover if a similar transformation could be performed using tetrahydrothiophene as a method to prepare 2-thio substituted pyridine derivatives. Reaction of 3-cyanopyridine *N*-oxide **1a** ($R^1 = 3-CN$) with 4-nitrobenzoyl chloride ($R^2 = 4-NO_2C_6H_4$, 2.2 equiv) and triethylamine (2.2 equiv) in tetrahydrothiophene (0.2 M) at 50 °C overnight did not give **3**, the analogous product to that observed using THF. Instead, the 2-substituted pyridine **4a** ($R^1 = 3-CN$) was isolated in an excellent 74% yield. Within this transformation, a chloride had been incorporated into the product rather than a

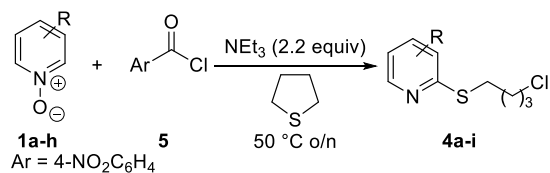
molecule of 4-nitrobenzoate. Introduction of the chloride group provided greater potential for further functionalization and we believed this represented a promising new transformation. Within this manuscript we describe the scope and limitations of this process, expand the transformation to encompass alternative nitrogen containing heterocycles and show the reaction can be performed effectively in ethereal solvents allowing a significant reduction in the amount of sulfide nucleophile used.

Scheme 1. Different Reactivity of Ethers and Thioethers



Having showed the reaction was effective using 3-cyano pyridine *N*-oxide **1a** as the substrate under the same conditions developed for the reaction of THF,¹² we went on to examine alternative pyridine *N*-oxide substrates (Table 1). Whilst 4-cyanopyridine *N*-oxide **1b** was a less effective substrate, the product was easily purified by column chromatography (entry 2; 28%). 3-Chloro and 4-chloropyridine *N*-oxide **1c** and **1d** also gave the expected products in 51% and 39% yield respectively (entries 3 and 4). In addition, the di-substituted substrate **1g** gave **4g** in an excellent 60% yield (entry 7) providing an improved entry to a scaffold known to be a potent TRPV1 antagonist.¹³ The transformation requires an electron withdrawing group on the pyridine to proceed (**1h**, entry 8), although in an extreme case (**4f**, entry 6), this prevents *O*-benzoylation, presumably due to the reduced nucleophilicity of the *N*-oxide. Blocking the 2-position of the pyridine ring resulted in *O*-benzoylation but this product did not lead to the 4-substituted derivative (entry 9).

Table 1. Reaction of Pyridine *N*-Oxide Substrates^a

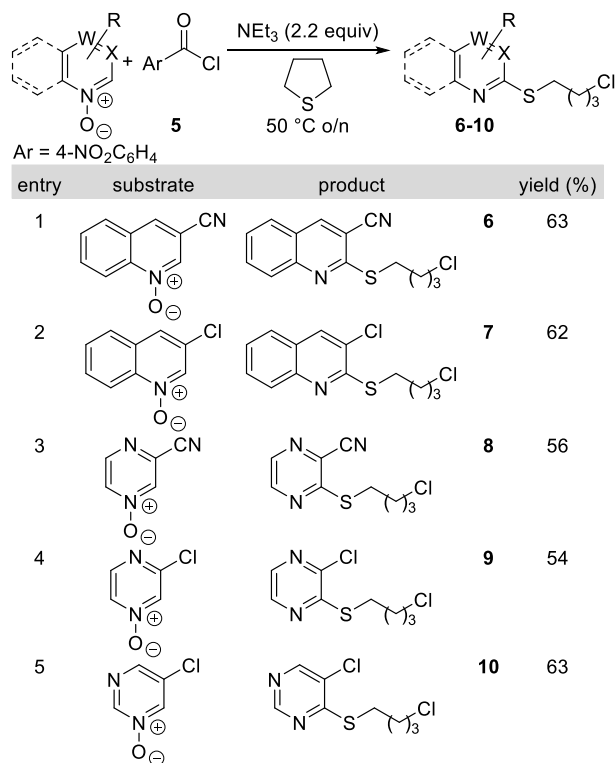


entry	N-oxide	R	product	yield (%) ^b
1	1a	3-CN	4a	74
2	1b	4-CN	4b	28
3	1c	3-Cl	4c	51
4	1d	4-Cl	4d	39
5	1e	3-NO ₂	4e	37
6	1f	4-NO ₂	4f	0 ^c
7	1g	2-CF ₃ ,5-CN	4g	60
8	1h	H	4h	0 ^d
9	1i	2-Cl, 6-Cl	4i	0 ^d

^aReactions carried out at 0.2 M concentration with 2.2 equiv of 4-nitrobenzoyl chloride. ^bIsolated yield. ^cStarting material recovered. ^dProduct of O-benzoylation observed.

Encouraged by the excellent reactivity shown by pyridine *N*-oxide substrates we went on to examine alternative nitrogen containing heterocycles within the transformation (Table 2). Electron deficient quinoline *N*-oxides smoothly delivered the 2-substituted products (entries 1 and 2). 1,4-Pyrazine *N*-oxides (entries 3 and 4) and a pyrimidine *N*-oxide (entry 5; 63%) were also effective substrates. The transformation therefore appears to be effective across a range of heterocyclic *N*-oxides leading to functionalized products with excellent opportunities for further elaboration.

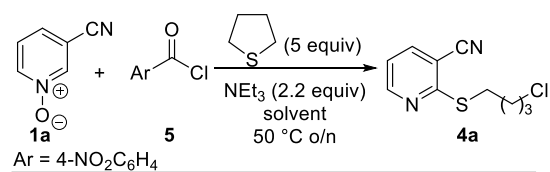
Table 2. Reaction of Alternative Heterocyclic *N*-Oxides



Despite the success observed in the reaction of the *N*-oxide substrates shown in Tables 1 and 2, a drawback of the overall transformation was using the sulfide as the reaction medium. This presented two distinct disadvantages to the process. First, the sulfide was used in vast excess; for example, in the reaction of tetrahydrothiophene with 3-cyanopyridine *N*-oxide **1a** the sulfide was present in a 57 equiv excess (Table 1, entry 1). Second, the transformation was limited to sulfides which were liquids at 50 °C. We therefore sought to discover if a suitable solvent could be found to overcome these challenges (Table 3). Toluene proved ineffective, returning only starting material after reaction at 50 °C overnight. Both acetonitrile (entry 2) and THF (entry 3) showed the presence of the desired product **4a** in the crude reaction mixture along with a number of unidentified co-products that incorporated the solvent.¹⁴ Given the promise of THF we postulated that a more hindered ether may prove effective as the solvent. We initially examined eucalyptol which gave the product in 26% isolated yield (entry 5). We also examined a series of acyclic ethers with different steric demands (entries 6–9). From this study, diisopropyl ether emerged as the most effective solvent which was easy to handle at the operating temperature of the reaction (entry

9; 53%). Whilst this gave the product in a lower yield than when using the sulfide as the reaction solvent (Table 1, entry 1; 74%) the reduction to 5 equiv of sulfide provided distinct benefits.

Table 3. Optimization of the Reaction Solvent^a

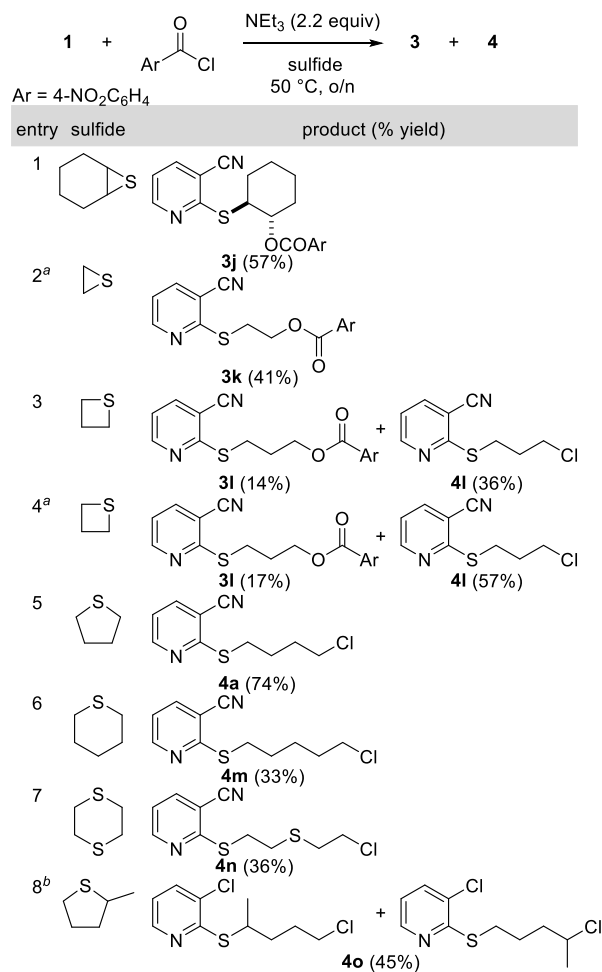


entry	solvent	yield (%) ^b
1	toluene	0
2	acetonitrile	not isolated
3	THF	not isolated
4	acetone	14
5	eucalyptol	26
6	<i>t</i> -butylmethyl ether	44
7	diethyl ether	51
8	dibutyl ether	42
9	diisopropyl ether	53

^aReactions carried out at 0.2 M concentration with 2.2 equiv of 4-nitrobenzoyl chloride. ^bIsolated yield.

Having discovered a suitable solvent with which to undertake the reaction we were able to explore the effect of changing the thioether substrate (Table 4). Crucially, adoption of a solvent allowed the use of solid thioether substrates (*e.g.* entry 7). Two key findings came from this part of the investigation. We were able to isolate products from the reaction of 3- and 4-membered thioethers which provided 2-substituted pyridine products (entries 1–3). This was in stark contrast to previous investigations where we were unable to isolate a product from the reaction using either epoxides or oxiranes.¹² In addition, the ring size of the nucleophilic sulfide dictated which product was obtained from the reaction. Using the strained cyclohexene sulfide (entry 1) and thiirane (entry 2), the product from the transformation was the 4-nitrobenzoate **3**. With less strained 5- and 6-membered ring sulfides as substrates the product was the corresponding chloride **4** (entries 5–8). Using thietane as the substrate gave mixtures of both the 4-nitrobenzoate **3** and the chloride product **4**, the ratio of which could be altered by changing the reaction temperature (entries 3 and 4).

Table 4. Alternative Thioether Substrates



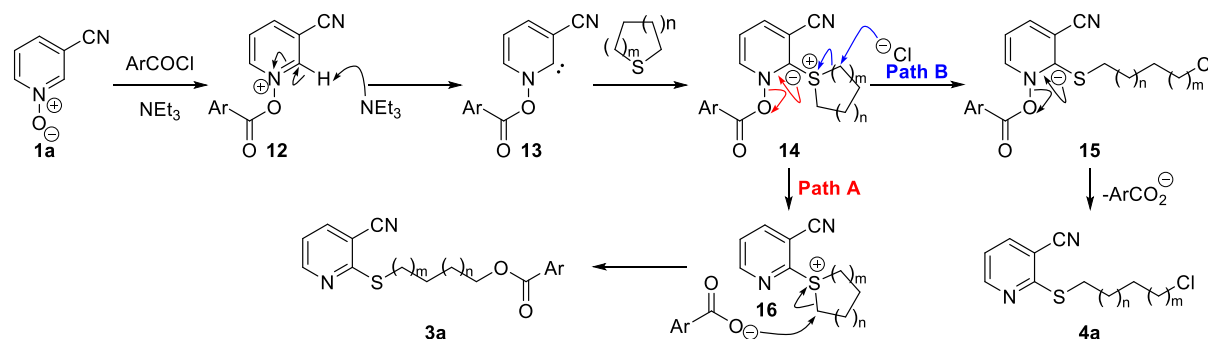
^aReaction carried out at 25 °C.

^bProduct isolated as an inseparable 1:1 mixture of regioisomers.

The unexpected change in reaction outcome based upon the structure of the sulfide is intriguing and provides insight into the reaction mechanism. A potential mechanistic course for the process is presented in Scheme 2. *O*-Benzoylation of **1a** followed by deprotonation leads to the carbene intermediate **13** which can combine with the sulfide to generate the ylide **14**. Sulfur ylides are more stable than their corresponding oxygen variants,¹⁵ which could provide the reason for the product divergence when changing from cyclic ethers to cyclic thioethers and the effect of different thioether substrates. Ylides derived from more strained sulfur nucleophiles will be less stable. Therefore, the reaction follows Path A, eliminating 4-nitrobenzoate followed by recombination through ring opening to give the product **3a**. Increasing the stability of the ylide through use of a less strained sulfide (Table 4, entries 5–8) slows down the elimination

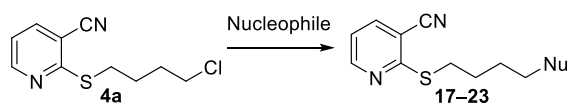
of 4-nitrobenzoate and allows selective ring opening with the more nucleophilic chloride ion leading to **4a** (Path B).¹⁶ Consistent with this proposal, in reactions where mixtures of **3a** and **4a** are observed reducing the temperature provides increased amounts of **4a** (Table 4, entries 3 and 4).

Scheme 2. Potential Mechanism for the Pyridine *N*-Oxide Functionalization



The introduction of a chloride instead of a 4-nitrobenzoate in the reaction products was unexpected at the start of this work, however, the chloride is an extremely versatile functional group (Table 5). We examined the addition of a series of nitrogen (entry 1; 97% and entry 2; 36%), oxygen (entry 3; 97%), sulfur (entry 4; 96% and entry 5; 34%), phosphorous (entry 6; 32%) and carbon nucleophiles (entry 7; 88%) to **4a** to explore the flexibility of the transformation in synthesis. Overall, the product from this novel coupling process provides an effective substrate for further transformations to introduce diversity.

Table 5. Functionalization of Pyridine Products



entry	nucleophile	product	yield (%)
1 ^a	NaN ₃	17	97
2 ^b	morpholine	18	36
3 ^c	NaOAc	19	97
4 ^d	KSac	20	96
5 ^e	4-MeOC ₆ H ₄ SH	21	34
6 ^f	P(OEt) ₃	22	32
7 ^g	KCN	23	88

^aNaN₃, DMF, 80 °C, 48 h. ^bMorpholine, rt, 48 h.

^cNaOAc, DMF, 80 °C 48 h. ^dKSac, KI, DMF, 80 °C, 48 h.

^e4-MeOC₆H₄CH₂SH, Cs₂CO₃, DMF, 80 °C, 48 h.

^fP(OEt)₃, 160 °C, 48 h. ^gKCN, KI, DMF, rt, 18 h.

In summary, we have developed a simple and effective method for the regioselective functionalization of heterocyclic *N*-oxides through reaction with 4-nitrobenzoyl chloride and a cyclic sulfide under basic conditions. The transformation proceeds in higher yields than the related process involving cyclic ethers and is tolerant of a greater range of substrates. Thioethers within a strained 3- or 4-membered ring provide access to an alternative ester product. It is believed the divergence in the reaction pathways is due to the formation of a less-stable ylide intermediate when using thiirane and thietane derivatives as the reactive sulfide. Thioethers are significantly more reactive than ethers within this transformation such that ethers are effective solvents for the reaction allowing the use of solid sulfides within the process. The products can be used in a variety of substitution reactions suggesting they could be useful in the formation of nitrogen containing heterocycles of pharmaceutical and agrochemical interest. For example, 2-thio substituted pyridine *N*-oxides have been shown to have antibiotic activity.¹⁷ We are currently engaged in exploiting this transformation in discovery research and will report on our findings in due course.

EXPERIMENTAL SECTION

General Procedure A. The appropriate pyridine *N*-oxide (1.0 equiv) and 4-nitrobenzoyl chloride (2.2 equiv) were added to a 20 mL flame-dried microwave vial. The pressure was carefully restored using a nitrogen/argon balloon. The appropriate cyclic thioether (0.2 M) was introduced, and the mixture cooled to 0 °C. Triethylamine (2.2 equiv) was added, with rapid stirring of the reaction mixture. Following completion of addition, the cooling bath was removed and the mixture stirred for 5 minutes at room temperature before heating to 50 °C overnight. Ethyl acetate (EtOAc) (5 mL) was added, the mixture transferred to a round-bottomed flask and the volatiles were removed under reduced pressure. Compounds were purified by flash column chromatography, eluting with the stated solvent systems.

General Procedure B. The appropriate pyridine *N*-oxide (1.0 equiv) and 4-nitrobenzoyl chloride (2.2 equiv) were added to a 20 mL flame-dried microwave vial. The pressure was carefully restored using a nitrogen/argon balloon. Diisopropyl ether (0.4 M) and the appropriate cyclic thioether (5.0 equiv) were introduced, and the mixture cooled to 0 °C. Triethylamine (2.2 equiv) was added, with rapid stirring of

the reaction mixture. Following completion of addition, the cooling bath was removed and the mixture stirred for 5 minutes at room temperature before heating to 50 °C overnight. EtOAc (5 mL) was added, the mixture transferred to a round-bottomed flask and the volatiles were removed under reduced pressure. Compounds were purified by flash column chromatography, eluting with the stated solvent systems.

2-((4-Chlorobutyl)thio)nicotinonitrile (**4a**). Following General Procedure A, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in tetrahydrothiophene (THT) (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the *title compound* **4a** (138 mg, 0.61 mmol, 74%) as a yellow oil. IR (ATR)/cm⁻¹ 3061, 2936, 2864, 2222, 1571, 1549, 1443, 1391; ¹H NMR (400 MHz, CDCl₃) δ 8.57 (dd, *J* = 4.9 Hz, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* = 7.7 Hz, *J* = 4.9 Hz, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 3.31 (t, *J* = 6.9 Hz, 2H), 1.99–1.86 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 163.0, 152.2, 140.7, 118.6, 115.6, 107.7, 44.5, 31.6, 29.4, 26.6; LRMS (ES + APCI) *m/z*: calcd. for C₁₀H₁₁³⁵ClN₂S 226.0; found 227.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₀H₁₂³⁵ClN₂S 227.0410; found 227.0408.

2-((4-Chlorobutyl)thio)isonicotinonitrile (**4b**). Following General Procedure A, 4-cyanopyridine *N*-oxide (100 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the *title compound* **4b** (52 mg, 0.23 mmol, 28%) as a yellow oil. IR (ATR)/cm⁻¹ 3050, 2925, 2853, 2237, 1584, 1530, 1458, 1365; ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, *J* = 5.1 Hz, 1H), 7.38–7.36 (m, 1H), 7.15 (dd, *J* = 5.1 Hz, *J* = 1.4 Hz, 1H), 3.57 (t, *J* = 6.3 Hz, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 1.97–1.83 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 161.5, 150.3, 124.0, 120.4, 120.0, 116.4, 44.5, 31.6, 29.3, 26.7; LRMS (ES + APCI) *m/z*: calcd. for C₁₀H₁₁³⁵ClN₂S 226.0; found 226.9 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₀H₁₂³⁵ClN₂S 227.0410; found 227.0406.

3-Chloro-2-((4-chlorobutyl)thio)pyridine (**4c**). Following General Procedure A, 3-chloropyridine *N*-oxide (108 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification

via flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the *title compound* **4c** (100 mg, 0.42 mmol, 51%) as a yellow oil. IR (ATR)/cm⁻¹ 3044, 2929, 2864, 1566, 1434, 1387; ¹H NMR (400 MHz, CDCl₃) δ 8.33 (dd, *J* = 4.7 Hz, *J* = 1.5 Hz, 1H), 7.53 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 6.95 (dd, *J* = 7.8 Hz, *J* = 4.7 Hz, 1H), 3.58 (t, *J* = 7.0 Hz, 2H), 3.23 (t, *J* = 7.0 Hz, 2H), 1.99–1.84 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 157.4, 147.1, 135.9, 129.3, 119.7, 44.6, 31.8, 29.3, 26.7; LRMS (ES + APCI) *m/z*: calcd. for C₉H₁₁³⁵Cl₂NS 235.0; found 235.9 [M+H]⁺; HRMS (ESI, +ve) *m/z*: [M+H]⁺ calcd. for C₉H₁₂³⁵Cl₂NS 236.0067; found 236.0063.

4-Chloro-2-((4-chlorobutyl)thio)pyridine (**4d**). Following General Procedure A, 4-chloropyridine *N*-oxide (107.5 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the *title compound* **4d** (77 mg, 0.33 mmol, 39%) as a yellow oil. IR (ATR)/cm⁻¹ 3042, 2933, 2864, 1562, 1540, 1452, 1355; ¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, *J* = 5.4 Hz, 1H), 7.18–7.16 (m, 1H), 6.97 (dd, *J* = 5.4 Hz, *J* = 1.9 Hz, 1H), 3.57 (t, *J* = 7.0 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 1.97–1.82 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 161.0, 150.1, 143.9, 122.0, 120.0, 44.6, 31.7, 29.4, 26.8; LRMS (ES + APCI) *m/z*: calcd. for C₉H₁₁³⁵Cl₂NS 235.0; found 235.9 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₉H₁₂³⁵Cl₂NS 236.0067; found 236.0063.

2-((4-Chlorobutyl)thio)-3-nitropyridine (**4e**). Following General Procedure A, 3-nitropyridine *N*-oxide (116 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 8:1 isocratic), afforded the *title compound* **4e** (75 mg, 0.30 mmol, 37%) as a yellow oil. IR (ATR)/cm⁻¹ 3076, 2931, 2860, 1584, 1554, 1510, 1396, 1329; ¹H NMR (400 MHz, CDCl₃) δ 8.68 (dd, *J* = 4.6 Hz, *J* = 1.7 Hz, 1H), 8.48 (dd, *J* = 8.2 Hz, *J* = 1.7 Hz, 1H), 7.19 (dd, *J* = 8.2 Hz, *J* = 4.6 Hz, 1H), 3.59 (t, *J* = 7.0 Hz, 2H), 3.26 (t, *J* = 7.0 Hz, 2H), 2.01–1.85 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) 158.1, 153.2, 142.3, 133.9, 118.7, 44.6, 31.9, 29.8, 26.2; LRMS (ES + APCI) *m/z*: calcd. for C₉H₁₁³⁵ClN₂O₂S 246.0; found 246.9 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₉H₁₂³⁵ClN₂O₂S 247.0308; found 247.0310.

5-Cyano-2-(trifluoromethyl)pyridine 1-oxide (**1g**).¹⁹ To a stirred mixture of 6-(trifluoromethyl)nicotinonitrile (1.00 g, 5.81 mmol) and urea-hydrogen peroxide addition complex (UHP) (1.15 g, 12.21 mmol) in CH₂Cl₂ (15 mL) was added trifluoroacetic anhydride (TFAA) (1.7 mL, 12.21 mmol) at 0 °C under argon. The reaction was allowed to stir at room temperature for 0.5 h. Excess peroxide was destroyed by the addition of 10% aqueous potassium iodide solution (50 mL). The organic phase was washed with saturated 10% aqueous Na₂S₂O₃ solution (50 mL) and water (50 mL), then dried over MgSO₄, and filtered. The filtrate was concentrated under reduced pressure before the residue was triturated by diethyl ether to afford the *title compound* **1g** as an off-white solid (571 mg, 3.04 mmol, 52%). m.p. 94–96 °C; IR (ATR)/cm⁻¹ 3031, 2988, 2243, 1605, 1549, 1389, 1277, 1155; ¹H NMR (500 MHz, CDCl₃) δ 8.49 (br s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 143.8, 126.0, 125.9–125.8 (m, 1C), 122.6, 119.2 (q, *J*_{FC} = 271.6 Hz), 115.8, 113.1; ¹⁹F NMR (471 MHz, CDCl₃) δ -69.6 (s, 3F); LRMS (ES + APCI) *m/z*: calcd. for C₇H₃F₃N₂O 188.0; found 187.1 [M-H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₇H₄F₃N₂O 189.0276; found 189.0274.

2-((4-Chlorobutyl)thio)-6-(trifluoromethyl)nicotinonitrile (**4g**). Following General Procedure A, compound **1g** (100 mg, 0.53 mmol) and 4-nitrobenzoyl chloride (218 mg, 1.17 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/CH₂Cl₂ 3:1 isocratic), afforded the *title compound* **4g** (94 mg, 0.32 mmol, 60%) as a yellow oil. IR (ATR)/cm⁻¹ 3079, 2940, 2869, 2230, 1579, 1361, 1333, 1143; ¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.33 (t, *J* = 6.5 Hz, 2H), 1.98–1.89 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 164.6, 150.2 (q, *J*_{FC} = 36.1 Hz, 1C), 142.3, 120.7 (q, *J*_{FC} = 273.9 Hz, 1C), 115.1 (q, *J*_{FC} = 2.8 Hz, 1C), 114.5, 110.4, 44.3, 31.6, 29.9, 26.5; ¹⁹F NMR (471 MHz, CDCl₃) δ -69.1 (s, 3F); LRMS (ES + APCI) *m/z*: calcd. for C₁₁H₁₀³⁵ClF₃N₂S 294.0; found 295.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₁H₁₁³⁵ClF₃N₂S 295.0284; found 295.0280.

2-((3-Cyanopyridin-2-yl)thio)cyclohexyl 4-nitrobenzoate (**3j**). Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and 7-thiabicyclo[4.1.0]heptane (476 mg, 4.17 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the *title compound* **3j** (182 mg, 0.48 mmol, 57%) as a yellow oil. IR (ATR)/cm⁻¹ 3050, 2933, 2856, 2224, 1720, 1571, 1525, 1391, 1346, 1264; ¹H NMR (500 MHz, CDCl₃) δ 8.62 (dd, *J* = 5.0 Hz, *J* = 1.5 Hz, 1H), 8.18 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.73 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H), 7.08 (dd, *J* = 8.0 Hz, *J* = 5.0 Hz, 1H), 5.19 (td, *J* = 9.0 Hz, *J* = 4.0 Hz, 1H), 4.43 (td, *J* = 9.0 Hz, *J* = 4.0 Hz, 1H), 2.37–2.23 (m, 2H), 1.90–1.66 (m, 4H), 1.61–1.51 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 163.8, 162.4, 152.1, 150.6, 140.9, 135.8, 130.8, 123.5, 119.0, 115.4, 108.1, 77.4, 75.9, 46.5, 31.3, 25.1, 23.4; LRMS (ES + APCI) *m/z*: calcd. for C₁₉H₁₇N₃O₄S 383.1; found 384.2 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₉H₁₈N₃O₄S 384.1018; found 384.1019.

2-((3-Cyanopyridin-2-yl)thio)ethyl 4-nitrobenzoate (**3k**). Following General Procedure B, with stirring at 25 °C overnight 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and thiirane (250 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the *title compound* **3k** (112 mg, 0.34 mmol, 41%) as off-white solid. m.p. 132–134 °C; IR (ATR)/cm⁻¹ 3109, 3078, 2921, 2853, 2224, 1714, 1608, 1569, 1525, 1391; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (dd, *J* = 4.9 Hz, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 7.83 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.11 (dd, *J* = 7.7 Hz, *J* = 4.9 Hz, 1H), 4.65 (t, *J* = 6.4 Hz, 2H), 3.70 (t, *J* = 6.4 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 164.6, 161.8, 152.3, 150.8, 141.0, 135.4, 130.9, 123.7, 119.2, 115.3, 107.9, 64.1, 28.7; LRMS (ES + APCI) *m/z*: calcd. for C₁₅H₁₁N₃O₄S 329.0; found 330.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₅H₁₂N₃O₄S 330.0543; found 330.0545.

3-((3-Cyanopyridin-2-yl)thio)propyl 4-nitrobenzoate (**3l**). Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and thietane (308

mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the *title compound* **3l** (48 mg, 0.14 mmol, 17%) as a yellow solid. m.p. 123–125 °C; IR (ATR)/cm⁻¹ 3113, 3081, 2957, 2933, 2220, 1716, 1607, 1567, 1519, 1385; ¹H NMR (400 MHz, CDCl₃) δ 8.52 (dd, *J* = 4.9 Hz, *J* = 1.8 Hz, 1H), 8.34–8.22 (m, 2H), 8.27–8.22 (m, 2H) 7.80 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 7.7 Hz, 4.9 Hz, 1H), 4.52 (t, *J* = 7.0 Hz, 2H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.26 (app quint, *J* = 7.0 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 164.7, 162.6, 152.2, 150.8, 140.8, 135.7, 130.9, 123.8, 118.8, 115.5, 107.8, 64.6, 28.6, 26.8; LRMS (ES + APCI) *m/z*: calcd. for C₁₆H₁₃N₃O₄S 343.1; found 344.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₆H₁₄N₃O₄S 344.0705; found 344.0708.

2-((3-Chloropropyl)thio)nicotinonitrile (**4l**). Following General Procedure B, with stirring at 25 °C overnight 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and thietane (308 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the *title compound* **4l** (100 mg, 0.47 mmol, 57%) as a yellow oil. IR (ATR)/cm⁻¹ 3063, 2955, 2222, 1571, 1551, 1441, 1391; ¹H NMR (400 MHz, CDCl₃) δ 8.57 (dd, *J* = 4.9 Hz, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.08 (dd, *J* = 7.7 Hz, *J* = 4.9 Hz, 1H), 3.60 (t, *J* = 7.0 Hz, 2H), 3.42 (t, *J* = 7.0 Hz, 2H), 2.20 (app quint, *J* = 7.0 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 162.6, 152.3, 140.7, 118.7, 115.5, 107.7, 43.5, 32.0, 27.4; LRMS (ES + APCI) *m/z*: calcd. for C₉H₉³⁵ClN₂S 212.0; found 212.9 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₉H₁₀³⁵ClN₂S 213.0248; found 213.0248.

2-((5-Chloropentyl)thio)nicotinonitrile (**4m**). Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and thiane (424 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 8:1 isocratic), afforded the *title compound* **4m** (66 mg, 0.28 mmol, 33%) as a yellow solid. m.p. 28–30 °C; IR (ATR)/cm⁻¹ 3059, 2988, 2949, 2925, 2853, 2224, 1571, 1545, 1391; ¹H NMR (400 MHz, CDCl₃) δ 8.57 (dd, *J* = 4.9 Hz, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* =

7.7 Hz, $J = 4.9$ Hz, 1H), 3.55 (t, $J = 7.0$ Hz, 2H), 3.28 (t, $J = 7.0$ Hz, 2H), 1.88–1.73 (m, 4H), 1.66–1.57 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.3, 152.2, 140.7, 118.5, 115.7, 107.7, 44.9, 32.2, 30.0, 28.6, 26.2; LRMS (ES + APCI) m/z : calcd. for $\text{C}_{11}\text{H}_{13}^{35}\text{ClN}_2\text{S}$ 240.0; found 241.1 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{14}^{35}\text{ClN}_2\text{S}$ 241.0566; found 241.0567.

2-((2-((2-Chloroethyl)thio)ethyl)thio)nicotinonitrile (**4n**). Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and 1,4-dithiane (500 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 7:1 isocratic), afforded the *title compound* **4n** (78 mg, 0.30 mmol, 36%) as an off-white solid. m.p. 58–60 °C; IR (ATR)/ cm^{-1} 3057, 2964, 2946, 2929, 2222, 1571, 1553, 1437, 1393; ^1H NMR (400 MHz, CDCl_3) δ 8.62 (dd, $J = 4.9$ Hz, $J = 1.8$ Hz, 1H), 7.82 (dd, $J = 7.7$ Hz, $J = 1.8$ Hz, 1H), 7.11 (dd, $J = 7.7$ Hz, $J = 4.9$ Hz, 1H), 3.75–3.69 (m, 2H), 3.48–3.42 (m, 2H), 3.04–2.98 (m, 2H), 2.90–2.85 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 162.3, 152.4, 140.9, 119.0, 115.4, 107.8, 43.1, 34.0, 31.6, 30.1; LRMS (ES + APCI) m/z : calcd. for $\text{C}_{10}\text{H}_{11}^{35}\text{ClN}_2\text{S}_2$ 258.0; found 259.0 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{12}^{35}\text{ClN}_2\text{S}_2$ 259.0130; found 259.0129.

2-((5-Chloropentan-2-yl)thio)nicotinonitrile and 2-((4-chloropentyl)thio)nicotinonitrile (**4o**). Following General Procedure B, 3-cyanopyridine *N*-oxide (100 mg, 0.83 mmol), 4-nitrobenzoyl chloride (339 mg, 1.83 mmol) and 2-methyltetrahydrothiophene (426 mg, 4.15 mmol) in diisopropyl ether (0.4 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the *title compound* **4o** (90 mg, 0.38 mmol, 45%) as a yellow oil in a 1:1 mixture of regioisomers. IR (ATR)/ cm^{-1} 3056, 2959, 2925, 2224, 1573, 1551, 1443, 1391; ^1H NMR (400 MHz, CDCl_3) δ 8.58–8.54 (m, 2H), 7.80–7.76 (m, 2H), 7.09–7.03 (m, 2H), 4.18–4.01 (m, 2H), 3.57 (t, $J = 6.4$ Hz, 1H), 3.32–3.26 (m, 3H), 2.04–1.80 (m, 8H), 1.52 (d, $J = 6.4$ Hz, 4H), 1.45 (d, $J = 6.4$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.3, 163.1, 152.2, 140.8, 140.7, 118.6, 118.5, 115.7, 107.7, 107.6, 58.2, 44.8, 39.8, 39.2, 33.8, 30.1, 29.7, 26.4, 25.5, 21.3 (2 C missing); LRMS (ES + APCI) m/z : calcd. for $\text{C}_{11}\text{H}_{13}^{35}\text{ClN}_2\text{S}$ 240.0; found 241.0 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{14}^{35}\text{ClN}_2\text{S}$ 241.0561; found 241.0562.

3-Cyanoquinoline *N*-oxide.¹⁸ *m*-Chloroperoxybenzoic acid (<77%, 1.35 g, 7.79 mmol) was added portion-wise to a solution of 3-cyanoquinoline (1.00 g, 6.49 mmol) in CH₂Cl₂ (17 mL) at 0 °C. Following completion of addition, the reaction mixture was stirred overnight at room temperature and subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with NaHCO₃ (50 mL) and brine (50 mL) before being dried, filtered and concentrated under reduced pressure. Further purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic), afforded the *title compound* as an off-white solid (473 mg, 2.78 mmol, 43%). m.p. 156–158 °C; IR (ATR)/cm⁻¹ 3042, 2936, 2237, 1580, 1495, 1372, 1331, 1229; ¹H NMR (500 MHz, CDCl₃) δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.60 (s, 1H), 8.05 (s, 1H), 7.98–7.90 (m, 2H), 7.78 (app t, *J* = 7.5 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 143.5, 134.9, 133.5, 130.6, 129.9, 129.2, 129.1, 120.2, 115.1, 107.3; LRMS (ES + APCI) *m/z*: calcd. for C₁₀H₆N₂O 170.1; found 171.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₀H₇N₂O 171.0558; found 171.0560.

2-((4-Chlorobutyl)thio)quinoline-3-carbonitrile (**6**). Following General Procedure A, 3-Cyanoquinoline *N*-oxide (100 mg, 0.59 mmol) and 4-nitrobenzoyl chloride (241 mg, 1.29 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 10:1 isocratic), afforded the *title compound* **6** (102 mg, 0.37 mmol, 63%) as a yellow oil. IR (ATR)/cm⁻¹ 3050, 2933, 2860, 2224, 1614, 1584, 1556, 1333; ¹H NMR (500 MHz, CDCl₃) δ 8.32 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.82–7.74 (m, 2H), 7.52 (ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, 1.0 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.05–1.93 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 158.7, 148.7, 142.6, 133.0, 128.4, 128.3, 126.8, 123.9, 115.9, 106.3, 44.5, 31.7, 29.5, 26.5; LRMS (ES + APCI) *m/z*: calcd. for C₁₄H₁₃³⁵ClN₂S 276.0; found 277.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₄H₁₄³⁵ClN₂S 277.0566; found 277.0570.

3-Chloroquinoline *N*-oxide.¹⁸ *m*-Chloroperoxybenzoic acid (<77%, 1.27 g, 7.36 mmol) was added portion-wise to a solution of 3-chloroquinoline (1.00 g, 6.13 mmol) in CH₂Cl₂ (16 mL) at 0 °C. Following

completion of addition, the reaction mixture was stirred overnight at room temperature and subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5×40 mL). The combined organic extracts were washed with NaHCO_3 (50 mL) and brine (50 mL) before being dried, filtered and concentrated under reduced pressure to afford the *title compound* as a pale yellow solid (1.04 g, 5.81 mmol, 95%). m.p. 118–120 °C; IR (ATR)/ cm^{-1} 3066, 2921, 2851, 1580, 1556, 1361, 1216; ^1H NMR (400 MHz, CDCl_3) δ 8.66 (d, $J = 8.4$ Hz, 1H), 8.51 (d, $J = 1.2$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.76–7.70 (m, 2H), 7.69–7.63 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 140.6, 135.5, 130.5, 129.9, 129.8, 127.6, 127.5, 124.5, 119.9; LRMS (ES + APCI) m/z : calcd. for $\text{C}_9\text{H}_6^{35}\text{ClNO}$ 179.0; found 179.9 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_7^{35}\text{ClNO}$ 179.0132; found 179.0133.

3-Chloro-2-((4-chlorobutyl)thio)quinoline (**7**). Following General Procedure A, 3-Chloroquinoline *N*-oxide (100 mg, 0.56 mmol) and 4-nitrobenzoyl chloride (229 mg, 1.23 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/ CH_2Cl_2 2:1 isocratic), afforded the *title compound* **7** (99 mg, 0.35 mmol, 62%) as a yellow oil. IR (ATR)/ cm^{-1} 3053, 2914, 2847, 1579, 1523, 1469, 1383; ^1H NMR (500 MHz, CDCl_3) δ 7.97 (s, 1H), 7.93 (d, $J = 8.5$ Hz, 1H), 7.68–7.62 (m, 2H), 7.45 (app t, $J = 7.0$ Hz, 1H), 3.63 (t, $J = 6.5$ Hz, 2H), 3.38 (t, $J = 6.5$ Hz, 2H), 2.05–1.94 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 157.5, 146.4, 133.9, 129.8, 128.0, 127.2, 126.9, 126.4, 126.1, 44.7, 31.9, 29.6, 26.6; LRMS (ES + APCI) m/z : calcd. for $\text{C}_{13}\text{H}_{13}^{35}\text{Cl}_2\text{NS}$ 285.0; found 285.9 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{13}\text{H}_{14}^{35}\text{Cl}_2\text{NS}$ 286.0224; found 286.0227.

3-Cyanopyrazine *N*-oxide.¹⁸ *m*-Chloroperoxybenzoic acid (<77%, 1.97 g, 11.42 mmol) was added portion-wise to a solution of pyrazine-2-carbonitrile (1.00 g, 9.51 mmol) in CH_2Cl_2 (25 mL) at 0 °C. Following completion of addition, the reaction mixture was stirred overnight at room temperature and subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5×40 mL). The combined organic extracts were washed with NaHCO_3 (50 mL) and brine (50 mL) before being dried, filtered and

concentrated under reduced pressure. Further purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic), afforded the *title compound* as an off-white solid (240 mg, 1.98 mmol, 21%). m.p. 140–142 °C; IR (ATR)/cm⁻¹ 3059, 3013, 2903, 2200, 1579, 1456, 1415, 1279; ¹H NMR (500 MHz, CDCl₃) δ 8.53 (d, *J* = 4.0 Hz, 1H), 8.37 (d, *J* = 1.5 Hz, 1H), 8.22 (dd, *J* = 4.0 Hz, *J* = 1.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 148.7, 138.3, 136.7, 134.2, 113.7; LRMS (ES + APCI) *m/z*: calcd. for C₅H₃N₃O 121.0; found 122.1 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₅H₄N₃O 121.0271; found 121.0270.

3-((4-Chlorobutyl)thio)pyrazine-2-carbonitrile (**8**). Following General Procedure A, 3-Cyanopyrazine *N*-oxide (100 mg, 0.83 mmol) and 4-nitrobenzoyl chloride (338 mg, 1.82 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 6:1 isocratic), afforded the *title compound* **8** (105 mg, 0.46 mmol, 56%) as a yellow oil. IR (ATR)/cm⁻¹ 3070, 2927, 2864, 2230, 1514, 1430, 1357, 1196; ¹H NMR (500 MHz, CDCl₃) δ 8.52 (d, *J* = 2.5 Hz, 1H), 8.32 (d, *J* = 2.5 Hz, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.29 (t, *J* = 6.5 Hz, 2H), 1.98–1.88 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 161.4, 146.0, 139.6, 128.4, 114.5, 44.3, 31.5, 29.4, 26.4; LRMS (ES + APCI) *m/z*: calcd. for C₉H₁₀³⁵ClN₃S 227.0; found 228.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₉H₁₁³⁵ClN₃S 228.0362; found 228.0366.

3-Chloropyrazine *N*-oxide.¹⁸ *m*-Chloroperoxybenzoic acid (<77%, 1.80 g, 10.50 mmol) was added portion-wise to a solution of 2-chloropyrazine (1.00 g, 8.73 mmol) in CH₂Cl₂ (23 mL) at 0 °C. Following completion of addition, the reaction mixture was stirred overnight at room temperature and subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with NaHCO₃ (50 mL) and brine (50 mL) before being dried, filtered and concentrated under reduced pressure. Further purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the *title compound* as an off-white solid (970 mg, 7.46 mmol, 85%). m.p. 97–99 °C; IR (ATR)/cm⁻¹ 3053, 3005, 2979, 1582, 1445, 1409, 1272; ¹H NMR (500 MHz,

CDCl₃) δ 8.25 (d, *J* = 4.0 Hz, 1H), 8.15 (d, *J* = 1.5 Hz, 1H), 8.01 (dd, *J* = 4.0 Hz, *J* = 1.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 151.9, 146.1, 133.7, 133.3; LRMS (ES + APCI) *m/z*: calcd. for C₄H₃³⁵ClN₂O 130.0; found 131.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₄H₄³⁵ClN₂O 130.9914; found 130.9915.

2-Chloro-3-((4-chlorobutyl)thio)pyrazine (**9**). Following General Procedure A, 3-Chloropyrazine *N*-oxide (100 mg, 0.77 mmol) and 4-nitrobenzoyl chloride (315 mg, 1.69 mmol) in THT (0.2 M), after purification *via* flash column chromatography (dry loading, petroleum ether/CH₂Cl₂ 3:1 isocratic), afforded the *title compound* **9** (98 mg, 0.42 mmol, 54%) as a yellow oil. IR (ATR)/cm⁻¹ 3046, 2927, 2866, 1528, 1497, 1432, 1337, 1143; ¹H NMR (500 MHz, CDCl₃) δ 8.29 (d, *J* = 2.5 Hz, 1H), 8.01 (d, *J* = 2.5 Hz, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 6.5 Hz, 2H), 1.99–1.85 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 156.6, 146.5, 141.8, 137.9, 44.5, 31.7, 29.6, 26.3 LRMS (ES + APCI) *m/z*: calcd. for C₈H₁₀³⁵Cl₂N₂S 236.0; found 236.4 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₈H₁₁³⁵Cl₂N₂S 237.0020; found 237.0024.

5-Chloropyrimidine *N*-oxide.¹⁸ *m*-Chloroperoxybenzoic acid (<77%, 1.81 g, 10.50 mmol) was added portion-wise to a solution of 5-chloropyrimidine (1.00 g, 8.73 mmol) in CH₂Cl₂ (23 mL) at 0 °C. Following completion of addition, the reaction mixture was stirred overnight at room temperature and subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with NaHCO₃ (50 mL) and brine (50 mL) before being dried, filtered and concentrated under reduced pressure. Further purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic), afforded the *title compound* as an off-white solid (874 mg, 6.72 mmol, 77%). m.p. 108–109 °C; IR (ATR)/cm⁻¹ 3026, 3003, 2879, 1569, 1519, 1406, 1249; ¹H NMR (500 MHz, CDCl₃) δ 8.85 (s, 1H), 8.39 (s, 1H), 8.19 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 148.1, 143.6, 142.2, 130.8; LRMS (ES + APCI) *m/z*: calcd. for C₄H₃³⁵ClN₂O 130.0; found 130.8 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₄H₄³⁵ClN₂O 131.0007; found 130.9996.

5-Chloro-4-((4-chlorobutyl)thio)pyrimidine (**10**). Following General Procedure A, 5-Chloropyrimidine *N*-oxide (100 mg, 0.77 mmol) and 4-nitrobenzoyl chloride (315 mg, 1.69 mmol) in THT (0.2 M), after

purification *via* flash column chromatography (dry loading, petroleum ether/CH₂Cl₂ 1:1 isocratic), afforded the *title compound* **10** (114 mg, 0.48 mmol, 63%) as a yellow oil. IR (ATR)/cm⁻¹ 3040, 2936, 2866, 1543, 1415, 1370, 1132; ¹H NMR (500 MHz, CDCl₃) δ 8.82 (s, 1H), 8.38 (s, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 6.5 Hz, 2H), 1.99–1.86 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 167.9, 155.3, 152.8, 128.9, 44.4, 31.7, 29.1, 26.5; LRMS (ES + APCI) *m/z*: calcd. for C₈H₁₀³⁵Cl₂N₂S 236.0; found 237.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₈H₁₁³⁵Cl₂N₂S 237.0020; found 237.0025.

2,6-Dichloropyridine *N*-oxide.¹⁸ *m*-Chloroperoxybenzoic acid (<77%, 1.40 g, 8.10 mmol) was added portion-wise to a solution of 2,6-dichloropyridine (1.00 g, 6.76 mmol) in CH₂Cl₂ (18 mL) at 0 °C. Following completion of addition, the reaction mixture was stirred overnight at room temperature and subsequently quenched with a saturated aqueous solution of potassium carbonate (30 mL). The resulting layers were separated before the aqueous layer was extracted with chloroform (5 × 40 mL). The combined organic extracts were washed with NaHCO₃ (50 mL) and brine (50 mL) before being dried, filtered and concentrated under reduced pressure. Further purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 5:1 isocratic), afforded the *title compound* as an off-white solid (420 mg, 2.58 mmol, 38%). m.p. 135–137 °C; IR (ATR)/cm⁻¹ 3081, 2960, 2866, 1532, 1447, 1365, 1264, 1143; ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 8.0 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 143.9, 125.2, 124.6; LRMS (ES + APCI) *m/z*: calcd. for C₅H₃³⁵Cl₂NO 163.0; found 164.1 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₅H₄³⁵Cl₂NO 163.9664; found 163.9662.

2-((4-Azidobutyl)thio)nicotinonitrile (**17**). A microwave vial, placed under an inert atmosphere, was charged with a solution of **4a** (50 mg, 0.22 mmol) in dimethylformamide (DMF) (0.9 mL). To this solution was added sodium azide (86 mg, 1.33 mmol). The reaction mixture was stirred at 80 °C for 48 hours before being cooled to room temperature. A 1:1 mixture of EtOAc/H₂O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to afford the *title compound* **17** (50 mg, 0.21 mmol, 97%) as a yellow oil. IR (ATR)/cm⁻¹ 3057, 2931, 2862, 2224,

1573, 1551, 1391; ^1H NMR (500 MHz, CDCl_3) δ 8.57 (dd, $J = 5.0$ Hz, $J = 2.0$ Hz, 1H), 7.79 (dd, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 7.07 (dd, $J = 8.0$ Hz, $J = 5.0$ Hz, 1H), 3.33 (t, $J = 7.0$ Hz, 2H), 3.29 (t, $J = 7.0$ Hz, 2H) 1.87–1.80 (m, 2H), 1.79–1.72 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.0, 152.2, 140.7, 118.6, 115.6, 107.7, 51.1, 29.6, 28.1, 26.6; LRMS (ES + APCI) m/z : calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_5\text{S}$ 233.1; found 234.0 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_5\text{S}$ 234.0808; found 234.0809.

2-((4-Morpholinobutyl)thio)nicotinonitrile (**18**). To a microwave vial, charged with compound **4a** (95 mg, 0.38 mmol), was added morpholine (60 μL , 0.66 mmol). The reaction mixture was stirred at room temperature for 48 hours. The solvent was removed under reduced pressure. A 1:1 mixture of EtOAc/ H_2O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude product. Further purification was performed *via* flash column chromatography (petroleum ether 1:1 EtOAc, isocratic) to afford the *title compound* **18** (38 mg, 0.14 mmol, 36%) as a yellow oil. IR (ATR)/ cm^{-1} 3072, 2934, 2853, 2804, 2222, 1573, 1549, 1391, 1166; ^1H NMR (500 MHz, CDCl_3) δ 8.55 (dd, $J = 5.0$ Hz, $J = 1.5$ Hz, 1H), 7.77 (dd, $J = 7.5$ Hz, $J = 1.5$ Hz, 1H), 7.05 (dd, $J = 7.5$ Hz, $J = 5.0$ Hz, 1H), 3.70 (t, $J = 5.0$ Hz, 4H), 3.29 (t, $J = 7.5$ Hz, 2H), 2.46–2.40 (m, 4H), 2.37 (t, $J = 7.5$ Hz, 2H), 1.81–1.73 (m, 2H), 1.69–1.62 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.4, 152.2, 140.7, 118.5, 115.7, 107.6, 67.1, 58.5, 53.8, 30.2, 27.2, 25.8; LRMS (ES + APCI) m/z : calcd. for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{OS}$ 277.1; found 278.1 $[\text{M}+\text{H}]^+$; HRMS (ESI-TOF) m/z : $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{OS}$ 278.1322; found 278.1323.

4-((3-Cyanopyridin-2-yl)thio)butyl acetate (**19**). To a microwave vial, charged with compound **4a** (100 mg, 0.44 mmol) in a solution of DMF (1.8 mL), was added sodium acetate (218 mg, 2.65 mmol). The reaction mixture was heated to 80 $^\circ\text{C}$ for 48 hours before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/ H_2O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the *title compound* **19** (107 mg, 0.43 mmol,

97%) as a yellow oil. IR (ATR)/cm⁻¹ 3065, 2946, 2864, 2224, 1731, 1573, 1549, 1391, 1233; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1H), 7.78 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.06 (dd, *J* = 8.0 Hz, *J* = 4.8 Hz, 1H), 4.13–4.08 (m, 2H), 3.32–3.28 (m, 2H), 2.05 (s, 3H), 1.84–1.77 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 171.3, 163.2, 152.2, 140.7, 118.6, 115.7, 107.7, 63.9, 29.8, 27.9, 25.9, 21.1; LRMS (ES + APCI) *m/z*: calcd. for C₁₂H₁₄N₂O₂S 250.1; found 251.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₂H₁₅N₂O₂S 251.0849; found 251.0850.

S-(4-((3-Cyanopyridin-2-yl)thio)butyl) ethanethioate (**20**). To a microwave vial, charged with compound **4a** (50 mg, 0.22 mmol) in a solution of DMF (1.1 mL), was added potassium thioacetate (152 mg, 1.32 mmol) and potassium iodide (8.2 mg, 0.04 mmol). The reaction mixture was heated to 80 °C for 48 hours before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H₂O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to afford the *title compound* **21** (56 mg, 0.21 mmol, 96%) as a yellow oil. IR (ATR)/cm⁻¹ 3063, 2923, 2851, 2222, 1683, 1571, 1549, 1391, 1138; ¹H NMR (400 MHz, CDCl₃) δ 8.56 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1H), 7.78 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.06 (dd, *J* = 7.6 Hz, *J* = 4.8 Hz, 1H), 3.27 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.85–1.69 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 195.9, 163.1, 152.2, 140.7, 118.6, 115.7, 107.6, 30.8, 29.6, 28.8, 28.6, 28.4; LRMS (ES + APCI) *m/z*: calcd. for C₁₂H₁₄N₂OS₂ 266.1; found 267.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₂H₁₅N₂OS₂ 267.0620; found 267.0621.

2-(((4-((4-Methoxyphenyl)thio)butyl)thio)nicotinonitrile (**21**). To a microwave vial, charged with compound **4a** (50 mg, 0.22 mmol) in a solution of DMF (1.1 mL), was added 4-methoxybenzenethiol (63 mg, 0.44 mmol) and caesium carbonate (216 mg, 0.66 mmol). The reaction mixture was heated to 80 °C for 48 hours before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H₂O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under

reduced pressure to afford the *title compound* **23** (25 mg, 0.08 mmol, 34%) as an off-white solid. m.p. 38–40 °C; IR (ATR)/cm⁻¹ 3066, 2949, 2830, 2220, 1571, 1553, 1493, 1395, 1235; ¹H NMR (400 MHz, CDCl₃) δ 8.55 (dd, *J* = 5.2 Hz, *J* = 1.6 Hz, 1H), 7.77 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.05 (dd, *J* = 7.6 Hz, *J* = 5.2 Hz, 1H), 6.83, (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 1.90–1.81 (m, 2H), 1.77–1.68 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 163.2, 159.1, 152.2, 140.7, 133.5, 126.4, 118.5, 115.7, 114.7, 107.6, 55.5, 35.5, 29.8, 28.4, 28.1; LRMS (ES + APCI) *m/z*: calcd. for C₁₇H₁₈N₂OS₂ 330.1; found 331.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₇H₁₉N₂OS₂ 331.0939; found 331.0936.

Diethyl 4-((3-cyanopyridin-2-yl)thio)butylphosphonate (**22**). To a microwave vial, charged with compound **4a** (50 mg, 0.22 mmol), was added triethyl phosphite (484 mg, 2.92 mmol). The reaction mixture was heated to 160 °C for 48 hours before being allowed to cool to room temperature. A 1:1 mixture of EtOAc/H₂O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. Further purification *via* flash column chromatography (dry loading, petroleum ether/EtOAc 3:1 isocratic), afforded the *title compound* **24** (23 mg, 0.07 mmol, 32%) as an orange oil. IR (ATR)/cm⁻¹ 3047, 2931, 2867, 2222, 1573, 1551, 1391, 1231, 1017, 956; ¹H NMR (500 MHz, CDCl₃) δ 8.56 (d, *J* = 4.0 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 7.5 Hz, *J* = 4.0 Hz, 1H), 4.18–4.02 (m, 4H), 3.27 (t, *J* = 6.0 Hz, 2H), 1.88–1.72 (m, 6H), 1.32 (t, *J* = 6.0 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 163.1, 152.2 (d, *J*_{PC} = 18.5 Hz, 1C), 140.7 (d, *J*_{PC} = 9.0 Hz, 1C), 118.6, 115.6, 107.6, 62.0–60.4 (m, 2C), 31.2–28.3 (m, 3C), 22.3 (d, *J*_{PC} = 107.5 Hz 1C), 16.6 (d, *J*_{PC} = 66.8 Hz, 2C); ³¹P NMR (202 MHz, CDCl₃) δ 35.2–28.5 (m, 1P); LRMS (ES + APCI) *m/z*: calcd. for C₁₄H₂₁N₂O₃PS 328.1; found 328.7 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₄H₂₂N₂O₃PS 329.1089; found 329.1087.

2-((4-Cyanobutyl)thio)nicotinonitrile (**23**). A microwave vial, placed under an inert atmosphere, was charged with a solution of **4a** (50 mg, 0.22 mmol) in DMF (0.8 mL). To this solution was added potassium cyanide (29 mg, 0.44 mmol) and potassium iodide (2.2 mg, 0.01 mmol). The reaction mixture was stirred

at room temperature for 18 hours. A 1:1 mixture of EtOAc/H₂O (10 mL) was added, the layers separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to afford the *title compound* **25** (42 mg, 0.19 mmol, 88%) as a yellow oil. IR (ATR)/cm⁻¹ 3055, 2936, 2856, 2243, 2222, 1571, 1551, 1391; ¹H NMR (400 MHz, CDCl₃) δ 8.57 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1H), 7.79 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.08 (dd, *J* = 7.6 Hz, *J* = 4.8 Hz, 1H), 3.30 (t, *J* = 6.8 Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.95–1.78 (m, 4H); ¹³C NMR (101 MHz, CDCl₃) δ 162.6, 152.3, 140.8, 119.4, 118.8, 115.5, 107.7, 29.0, 28.4, 24.5, 16.9; LRMS (ES + APCI) *m/z*: calcd. for C₁₁H₁₁N₃S 217.1; found 218.0 [M+H]⁺; HRMS (ESI-TOF) *m/z*: [M+H]⁺ calcd. for C₁₁H₁₂N₃S 218.0746; found 218.0744.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-Ray data for 3-chloropyrazine-1-oxide and NMR spectra for all compounds reported (PDF).

Corresponding Author

*E-Mail: Nicholas.Tomkinson@strath.ac.uk

ORCID

Nicholas C. O. Tomkinson: 0000-0002-5509-0133

ACKNOWLEDGMENT

The authors thank CRUK and the EPSRC for financial support and the EPSRC Mass Spectrometry Service, Swansea, for high-resolution spectra.

REFERENCES

- (1) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274. (b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.
- (2) Pyridines: (a) Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052–12062. (b) Henry G. D. *Tetrahedron* **2004**, *60*, 6043–6061.

(3) Quinolines: Batista, V. F.; Pinto, D. C. G. A.; Silva, A. M. S. *ACS Sustainable Chem. Eng.* **2016**, *4*, 4064–4078.

(4) Pyrazine and pyrimidines: (a) Wu, X.-F.; Wang, Z. *Transition Metal Catalyzed Pyrimidine, Pyrazine, Pyridazine and Triazine Synthesis* Elsevier B. V., 2017. (b) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319.

(5) For selected recent contributions to the area see: (a) Spahn, N. A.; Nguyen, M. H.; Renner, J.; Lane, T. K.; Louie, J. *J. Org. Chem.* **2017**, *82*, 234–242. (b) Ye, F.; Haddad, M.; Ratovelomanana-Vidal, V.; Michelet, V. *Org. Lett.* **2017**, *19*, 1104–1107. (c) Bugaenko, D. I.; Yurovskaya, M. A.; Karchava, A. V. *J. Org. Chem.* **2017**, *82*, 2136–2149. (d) Keylor, M. H.; Niemeyer, Z. L.; Sigman, M. S.; Tan, K. L. *J. Am. Chem. Soc.*, **2017**, *139*, 10613–10616. (e) Ali, W.; Dahiya, A.; Pandey, R.; Alam, T.; Patel, B. K. *J. Org. Chem.* **2017**, *82*, 2089–2096. (f) Lan, X.-B.; Li, Y.; Li, Y.-F.; Shen, D.-S.; Ke, Z.; Liu, F.-S. *J. Org. Chem.* **2017**, *82*, 2914–2925.

(6) For selected recent contributions to the area see: (a) Wang, D.; Wang, Y.; Zhao, J.; Shen, M.; Hu, J.; Liu, Z.; Li, L.; Xue, F.; Yu, P. *Org. Lett.* **2017**, *19*, 984–987. (b) Fier, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 9499–9502. (c) Yang, X.; Hu, F.; Wang, Y.; Yang, C.; Zou, X.; Liu, J.; Zhang, Q. *Chem. Commun.* **2017**, *53*, 7497–7500. (d) Takise, R.; Isshiki, R.; Muto, K.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2017**, *139*, 3340–3343. (e) Duret, G.; Quinlan, R.; Yin, B.; Martin, R. E.; Bissret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. *J. Org. Chem.* **2017**, *82*, 1726–1742. (f) Zhai, Y.; Chen, X.; Zhou, W.; Fan, M.; Lai, Y.; Ma, D. *J. Org. Chem.* **2017**, *82*, 4964–4969.

(7) For example see: Sreedhar, B.; Reddy, P. S.; Reddy, M. *Synthesis* **2009**, 1732–1738.

(8) Londregan, A. T.; Jennings, S.; We, L. *Org. Lett.* **2011**, *13*, 1840–1843.

(9) (a) Sumunnee, L.; Buathongjan, C.; Pimpasri, C.; Yotphan, S. *Eur. J. Org. Chem.* **2017**, 1025–1032. (b) Fu, W.-K.; Sun, K.; Qu, C.; Chen, X.-L.; Qu, L.-B.; Bi, W.-Z.; Zhao, Y.-F. *Asian J. Org. Chem.* **2017**, *6*, 492–495. (c) Wang, R.; Zeng, Z.; Chen, C.; Yi, N.; Jiang, J.; Cao, Z.; Deng, W.; Xiang, J. *Org. Biomol.*

Chem. **2016**, *14*, 5317–5321. (d) Du, B.; Qian, P.; Wang, Y.; Mei, H.; Han, J.; Pan, Y. *Org. Lett.* **2016**, *18*, 4144–4147.

(10) Su, Y.; Zhou, X.; He, C.; Zhang, W.; Ling, X.; Xiao, X. *J. Org. Chem.* **2016**, *81*, 4981–4987.

(11) a) Sun, K.; Chen, X.-L.; Li, X.; Qu, L.-B.; Bi, W.-Z.; Chen, Xi; Ma, Hui-Li; Zhang, S.-T.; Han, B.-W.; Zhao, Y.-F.; Li, C.-J. *Chem. Commun.* **2015**, *51*, 12111–12114. (b) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y. *Org. Lett.* **2013**, *15*, 1270–1273.

(12) Jones, D. H.; Kay, S. T.; McLellan, J. A.; Kennedy, A. R.; Tomkinson, N. C. O. *Org. Lett.* **2017**, *19*, 3512–3515.

(13) Tran, P.-T.; Kim, H. S.; Ann, J.; Kim, S.-E.; Kim, C.; Hong, M.; Hoang, V.-H.; Ngo, V. T. H.; Hong, S.; Cui, M.; Choi, S.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2326–2330.

(14) For a related reaction involving acetonitrile see: Tagawa, Y.; Tanaka, J.; Hama, K.; Goto, Y.; Hamana, M. *Tetrahedron Lett.* **1996**, *37*, 69–72. For a related reaction involving THF see reference 12.

(15) Nitrogen, Oxygen, and Sulfur Ylide Chemistry: A Practical Approach in Chemistry; Clarke, J. S., Ed.; Oxford University Press: Oxford, 2002.

(16) Kiyooka, S.-i.; Kaneno, D.; Fujiyama, R. *Tetrahedron* **2013**, *69*, 4247–4258.

(17) O'Donnell, G.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. *J. Nat. Prod.* **2009**, *72*, 360–365.

(18) Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310–2313

(19) Kiss, L. E.; Ferreira, H. S.; Torraot, L.; Bonifaciot, M. J.; Palma, P. N.; Soares-da-Silva, P.; Learmonth, D. A. *J. Med. Chem.* **2010**, *53*, 3396–3411.